UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,980	07/02/2001	Hiroshi Susaki	P20953	1881

7055 7590 08/22/2002

GREENBLUM & BERNSTEIN, P.L.C.
1941 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/22/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,980	Applicant(s) SUSAKI ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/2/01, 10/9/01, 2/19/02, 06/28/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,27-33,36 and 37* is/are rejected.

7)☒ Claim(s) *26, 34, 35, and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election without traverse of the sequence Gly-Gly-Phe-Gly in Paper No. 14 is acknowledged.

Applicants have requested that the non-elected sequence be rejoined upon allowance of a generic claim. However, because the election is a result of a restriction between patentably distinct sequences, rejoinder is not permitted. In order to expedite prosecution of this application, it is recommended that in the response to this Office action, Applicants delete any recitation in the claims of the non-elected sequence.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

3. The abstract of the disclosure is objected to because the meaning of the abbreviation "DDS" needs to be inserted into the abstract. Correction is required. See MPEP § 608.01(b).

4. The disclosure is objected to because of the following informalities: SEQ ID NOS need to be inserted after every occurrence of an amino acid sequence subject to the sequence

disclosure rules, e.g., at pages 7, 8, 14, 28-30, 38, 39, 42, and 44-49. See 37 CFR 1.821(d). At page 7, last line, "tetrapeptide" is misspelled. At page 13, line 20, the reference in the specification to a specific claim number should be deleted because of the likelihood of amendments to the claims and/or re-numbering of the claims by the time an application is allowed. At page 22, line 4, the letter "s" appears to be a misspelling. Appropriate correction is required.

5. Claims 33, 34, 37, and 38 are objected to because of the following informalities: SEQ ID NOS need to be inserted after every occurrence of an amino acid sequence subject to the sequence disclosure rules, e.g., in claims 33, 34, and 37. See 37 CFR 1.821(d). Appropriate correction is required.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 24, 25, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by the European Patent Application 0 712 635. The European Patent Application '635 teaches Mafenide, a drug, bound through a spacer and a cleavable group comprising the tetrapeptide Ala-Ala-Pro-Val to an alginate gel having carboxyl groups, which is a polymer carrier. See the Abstract and Example 8. The immobilized drug is treated with an aqueous solution comprising elastase, which results in release of the Mafenide into a supernatant. See Test Example 3. The European Patent Application '635 in Example 9 and Test Example 4 teach a similar assay using acrinol as the drug and a supernatant from a P. aeruginosa culture, which corresponds to Applicants' claimed biological sample. Examples 10-12 and Test Example 5 of the European Patent Application '635 use gentamycin and Norfloxacin as the drug. With respect to instant claims 27-29, the European Patent Application '635 does not teach the exact cleavage site for its immobilized drugs. However, there are only two possible cleavage sites: (1) between the drug and the cleavable group, in which case Applicants' claim 27 is inherently anticipated by the Test Examples of the reference; or (2) at a point within the cleavable group, in which case at least Applicants' claim 28 and possibly Applicants' claim 29 are inherently anticipated by the Test

Examples. Sufficient evidence of similarity is deemed to be present between the Test Examples of the European Patent Application '635 and Applicants' invention of claims 27-29 to shift the burden to Applicants to provide evidence that the claimed invention is unobviously different than the Test Examples of the European Patent Application '635.

8. Claim 32 is rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application 0 712 635. Application of the European Patent Application '635 is the same as in the above rejection of claims 24, 25, and 27-30. The European Patent Application '635 teaches in general that the drugs of its invention can be anti-cancer agents and anti-inflammatory agents (see, e.g., page 7, line 59; page 8, lines 5-7; and page 8, line 56 - page 9, line 15), and teaches in vitro drug release assays in which the drug is an antibiotic, but does not teach such assays in which the drug is an antineoplastic agent or an anti-inflammatory agent. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to perform the in vitro drug release assays of the European Patent Application '635 in which the drug is an anti-cancer agent or an anti-inflammatory agent, because the European Patent Application '635 teaches that anti-cancer agents and anti-inflammatory agents can usefully be immobilized on polymer gels, and because it would have been desirable and routine to test the products of such immobilization for their intended activity and efficacy.

9. Claim 36 is rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application 0 712 635 as applied against claim 32 above, and further in view of the Japanese Patent Application 6-87746. The European Patent Application '635 teaches the use of anti-cancer agents in general, but does not teach the specific drug of Applicants' claim 36. The Japanese Patent Application '746 teaches the drug of Applicants' claim 36 to be a useful

antitumor agent having activity against a variety of cancers. See, e.g., the Abstract. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to immobilize the antitumor agents of the Japanese Patent Application '746 on the polymer gels according to the method of the European Patent Application '635 because the antitumor agents of the Japanese Patent Application '746 are generically embraced by the European Patent Application '635 and because immobilization of the specific antitumor agents of the Japanese Patent Application '746 on the polymer gels of the European Patent Application '635 would have been expected to result in a product with activity against a wide variety of cancers.

10. Claim 1-11, 15-18, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 97/46260. (The examiner relies upon the European Patent Application 0 916 348 as a translation of the WO Patent Application '260. All citations in the rejection will use the page, line, and claim numbers of the European Patent Application '348). With respect to claim 21, the WO Patent Application '260 teaches a carboxy(C_{1-4})alkyldextran polyalcohol. See, e.g., the Abstract and claims 1 and 20. Note that an intended use limitation does not impart patentability to a product which is otherwise anticipated by the prior art. With respect to claims 22 and 23, the WO Patent Application '260 teaches doxorubicin bound through a cleavable tetrapeptide spacer to the carboxy(C_{1-4})alkyldextran polyalcohol (see, e.g., page 6, lines 19-22), and doxorubicin is a saccharide compound. With respect to instant claims 1-11 and 15-18, the doxorubicin complexes of the WO Patent Application '260 anticipate the claims because the doxorubicin corresponds both to the saccharide compound and the residue of a drug compound required by Applicants' claims. The claims contain no limitations excluding the

possibility that the saccharide compound and the residue of a drug compound have the same chemical identity.

11. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 97/46260 as applied against claims 1-11, 15-18, and 21-23 above, and further in view of the Japanese Patent Application 6-87746 and Theodore et al (U.S. Patent No. 5,886,143), the Gonsho et al article, the Hashida et al article, the Kichler et al article, or the Nishikawa et al article. The WO Patent Application '260 does not teach a saccharide compound different from the drug compound bound to the carboxy(C_{1-4})alkyldextran polyalcohol carrier. In particular, the WO Patent Application '260 teaches drug complexes comprising the drug of Applicants' claim 19 (see, e.g., page 5, lines 21-24; page 14, line 36; and claims 7, 14, and 19), which the Japanese Patent Application '746 describes as being useful for treating cancer of the liver (see, e.g., the Abstract), but does not teach incorporating a galactose, galactosamine, or N-acetylgalactosamine residue or cluster thereof into the drug complexes. Theodore et al teach binding hexose clusters and active agents onto polymeric carriers so that the active agents can be targeted for the treatment of liver conditions (see, e.g., column 1, lines 46-64; column 2, lines 27-41; and column 5, lines 13-27). Preferred hexoses include galactose, N-galactosamine, and N-acetylgalactosamine (see, e.g., column 19, lines 44-61 and claim 2). The Gonsho et al article teaches attaching galactose- terminated saccharides such as galactose and N-acetylgalactosamine to a poly(amino acid) in order to form a drug delivery system which targets the liver (see, e.g., the Abstract and page 281, column 2, last paragraph). The Hashida et al article teaches the targeted delivery of drugs and proteins to the liver by attaching galactose moieties to drug carriers (see, e.g., the Abstract; page 129, first paragraph; and page 135, paragraph bridging

columns 1 and 2). The Kichler et al article teaches galactose clusters for conjugation to bioactive (macro) molecule carrier systems for targeting the carriers to hepatocytes (see, e.g., the Abstract). The Nishikawa et al article teaches attaching galactose and mannose residues to a carboxymethyl-dextran drug carrier so that a drug conjugated to the carrier can be targeted to liver cells without affinity to other tissues (see, e.g., the Abstract). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to attach galactose or mannose residues to the drug complexes of the WO Patent Application '260 comprising the drug of Applicants' claim 19 because the Japanese Patent Application '746 discloses that the drug is useful in treating cancer of the liver and because Theodore et al, the Gonsho et al article, the Hashida et al article, the Kichler et al article, and the Nishikawa et al article teach that attachment of various galactose or mannose residues to polymeric drug carriers is a known and conventional method for targeting drugs to the organ to be treated. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal galactose or mannose residue:carrier ratios for the above-outlined drug complexes because Theodore et al (see, e.g., column 6, line 15 - column 7, line 16; column 28, lines 18-19), the Hashida et al article (see, e.g., page 133, column 2, second paragraph), and the Gonsho et al article (see, e.g., page 280, Figure 7 and column 2) disclose this ratio to be an art-recognized result-effective variable.

12. Claims 24, 27-33, 36, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 97/46260 as applied against claims 1-11, 15-18, and 21-23 above, and further in view of the European Patent Application 0 712 635. The WO Patent Application

'260 teaches complexes of drugs, including the drug of Applicants' claim 36, bound through a cleavable amino acid or peptide spacer to a carboxy(C_{1-4})alkyldextran polyalcohol (see, e.g., claim 14), but does not teach measuring the release of the drugs from the complexes in an enzyme assay. The European Patent Application '260 teaches measuring the release of immobilized drugs with in vitro enzyme assays (see, e.g., Test Examples 3-5). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to test the drug complexes of the WO Patent Application '260 with the in vitro enzyme assays of the European Patent Application '635 because both references involve drugs immobilized through cleavable peptide spacers where the drugs are to be released in vivo through action of an enzyme, and because the European Patent Application '635 shows that it is desirable and routine to test the products of such immobilization for their intended activity and efficacy.

13. Claims 26 and 35 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 34 and 38 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and to overcome the claim objections set forth in paragraph 5 above. With respect to instant claim 26, the prior art forms its polymer carriers knowing at the time of synthesis what their drug residue contents are, and accordingly there is no motivation to perform the claimed assay in order to measure the drug residue content of the DDS compound. With respect to instant claim 34, the prior art of record does not teach or suggest the -NH-Y'-CH_2-O-CO- portion of the recited spacer. With respect to instant claims 35 and 38, the enzymes recited in these claims are not associated with tumors or cancers, and therefore there would be no motivation to use them in

the assay method of the European Patent Application 0 712 635 to model drug release in the presence of tumors or cancers.

The Japanese Patent Application 8-319317 has been carefully considered but is not applied against the instant claims. There is not deemed to be motivation to combine the Japanese Patent Application '317 with the WO Patent Application 97/46260 as proposed in the International Preliminary Examination Report because of the disparate utilities for the two references, the former involving cell recovery and culture and the latter involving in vivo treatment.

14. Concerning References 13-16 on page 2 of the Information Disclosure Statement filed October 9, 2001, the examiner relies upon page 2, last paragraph, of Applicants' specification as the concise explanation of relevance required by 37 CFR 1.98(a)(3)(i).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1653

JRussel
August 21, 2002